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Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ			
L45	l43 and DNA vaccine	17	L45
L44	L43 same DNA vaccine	0	L44
L43	L42 with l38	82	L43
L42	adjuvant	101129	L42
L41	l39 and l11	39	L41
L40	L39 same l4	23	L40
L39	L38 same l2	2216	L39
L38	l35 not liposome	23297	L38
L37	l35 same l33	39	L37
L36	L35 with l33	14	L36
L35	L34 or l8	25061	L35
L34	$ammonium bromide	21712	L34
L33	l4 with l2	19978	L33
L32	L31 and l11	82	L32
L31	L30 same l4	99	L31

L30	L29 same l2	1929	L30
L29	l6 with l1	9153	L29
L28	L27 and l17	11	L28
L27	l26 and l5	133	L27
L26	supercoiled	3014	L26
L25	cationic lipid and l24	481	L25
L24	l6 and l23	739	L24
L23	L22 and l11	846	L23
L22	L21 same l5	989	L22
L21	l20 or l19	625696	L21
L20	matrix	610202	L20
L19	microparticle	23413	L19
L18	L17 same l5	18	L18
L17	PLGA	3863	L17
L16	l15 and l14	302	L16
L15	micron	497664	L15
L14	L13 and l12	623	L14
L13	diameter	2661824	L13
L12	L11 and l5	1564	L12
L11	vaccine or gene therapy	86422	L11
DB=EPAB; PLUR=YES; OP=ADJ			
L10	WO-9401102-A1.did.	1	L10
DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ			
L9	L8 and l7	10	L9
L8	cetyltrimethylammonium	4412	L8
L7	L6 same l5	67	L7
L6	stabili$	1804300	L6
L5	L4 with l3	2680	L5
L4	dna or nucleic or plasmid or polynucleotide or gene	379982	L4
L3	L2 with l1	15916	L3
L2	polymer or microparticle or capsule or microcapsule or nanoparticle or microsphere	1971605	L2
L1	lipid or $ammonium bromide or cationic lipid or phospholipid or phosphatidylcholine or lecithin	165576	L1

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L9: Entry 2 of 10 File: PGPB Jan 2, 2003

DOCUMENT-IDENTIFIER: US 20030003055 A1
TITLE: Methods of preparing gaseous precursor-filled microspheres

Detail Description Paragraph:
[0133] In addition, examples of compounds used to make mixed systems include, but by no means are limited to lauryltrimethylammonium bromide (dodecyl-), cetyltrimethylammonium bromide (hexadecyl-), myristyltrimethylammonium bromide (tetradecyl-), alkyldimethylbenzylammon- ium chloride (alkyl=C12,C14,C16), benzyldimethyldodecylammonium bromide/chloride, benzyldimethylhexadecylammonium bromide/chloride, benzyldimethyltetradecylammonium bromide/chloride, cetyldimethylethylammonium bromide/chloride, or cetylpyridinium bromide/chloride. Likewise perfluorocarbons such as pentafluoro octadecyl iodide, perfluorooctylbromide (PFOB), perfluorodecalin, perfluorododecalin, perfluorooctyliodide, perfluorotripropylamine, and perfluorotributylamine. The perfluorocarbons may be entrapped in liposomes or stabilized in emulsions as is well know in the art such as U.S. Pat. No. 4,865,836. The above examples of lipid suspensions may also be sterilized via autoclave without appreciable change in the size of the suspensions.

Detail Description Paragraph:
[0134] If desired, either anionic or cationic lipids may be used to bind anionic or cationic pharmaceuticals. Cationic lipids may be used to bind DNA and RNA analogues with in or on the surface of the gaseous precursor-filled microsphere. A variety of lipids such as DOTMA, N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride; DOTAP, 1,2-dioleoyloxy-3-(trimethylammonio)propane; and DOTB, 1,2-dioleoyl-3-(4'-trimethyl-ammonio)butanoyl-sn-glycerol may be used. In general the molar ratio of cationic lipid to non-cationic lipid in the liposome may be, for example, 1:1000, 1:100, preferably, between 2:1 to 1:10, more preferably in the range between 1:1 to 1:2.5 and most preferably 1:1 (ratio of mole amount cationic lipid to mole amount non-cationic lipid, e.g., DPPC). A wide variety of lipids may comprise the non-cationic lipid when cationic lipid is used to construct the microsphere. Preferably, this non-cationic lipid is dipalmitoylphosphatidylcholine, dipalmitoylphosphatidylethanolamine or dioleoylphosphatidylethanolamine. In lieu of cationic lipids as described above, lipids bearing cationic polymers such as polylysine or polyarginine may also be used to construct the microspheres and afford binding of a negatively charged therapeutic, such as genetic material, to the outside of the microspheres. Additionally, negatively charged lipids may be used, for example, to bind positively charged therapeutic compounds. Phosphatidic acid, a negatively charged lipid, can also be used to complex DNA. This is highly surprising, as the positively charged lipids were heretofore thought to be generally necessary to bind genetic materials to liposomes. 5 to 10 mole percent phosphatidic acid in the liposomes improves the stability and size distribution of the gaseous precursor-filled liposomes.

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L7: Entry 31 of 67 File: PGPB Dec 5, 2002

DOCUMENT-IDENTIFIER: US 20020182249 A1
TITLE: Preparation of stable formulations of lipid-nucleic acid complexes for efficient in vivo delivery

Detail Description Paragraph:
[0050] It was also a surprising discovery that lipid:nucleic acid complexes combined with a hydrophilic polymer attached to an amphipathic lipid (e.g., PEG-PE) also show an increased shelf life. Without being bound by a particular theory, it is believed that when the cationic lipid:DNA complex ("CLDC") is contacted with the hydrophilic polymer, the hydrophilic polymer locates and is incorporated into hydrophobic pockets in the complex via its hydrophobic side chains, while leaving the hydrophilic part at the exterior surface, thereby stabilizing the entire complex.

Detail Description Paragraph:
[0072] It has been established recently that PEG-PE incorporation in liposomes produces steric stabilization resulting in longer circulation times in blood (Allen et al., Biochim. Biophys. Acta 1066: 29-36 (1991); Papahadjopoulos et al., Proc. Natl. Acad. Sci. USA 88: 11460-11464 (1991)). In the present invention, inserting PEG-PE (e.g., 1% of total lipid) into the freshly formed lipid:nucleic acid complexes prevents the complexes from aggregating during storage. It was a surprising discovery, however, that the incorporation of PEG-PE did not inhibit transfection activity in vivo and also that the in vitro transfection activity, which was inhibited, was regained by the incorporation of Fab' fragment conjugated at the end of the PEG-PE. The presence of hydrophilic polymers in the lipid:nucleic acid complex provides increased shelf life, as measured by transfection efficiency after storage. Thus, it is desirable to add a hydrophilic polymer such as polyethylene glycol (PEG)-modified lipids or ganglioside G.sub.M1 to the liposomes. PEG may also be derivatized with other amphipathic molecules such as fatty acids, sphingolipids, glycolipids, and cholesterol. Addition of such components prevents liposome aggregation during coupling of the targeting moiety to the liposome. These components also provides a means for increasing circulation lifetime of the lipid:nucleic acid complexes.

Detail Description Paragraph:
[0097] It was a discovery of this invention that stabilized lipid:nucleic acid complexes (e.g., having condensed nucleic acid and/hydrophilic polymer) tended not to form visible large aggregates and had increased transfection efficiency and shelf life. Nucleic acid/liposome ratios for preparing lipid:nucleic acid complexes that do not form visible large aggregates can be determined by one of skill in the art. Typically, the ratio is determined by mixing fixed amounts of a nucleic acid, e.g., a plasmid, to various amounts of liposomes (see Example 1). In general, lipid:nucleic acid complexes are formed by pipetting the nucleic acid (e.g., plasmid DNA) into a liposome suspension of equal volume and mixing rapidly. Routinely, liposomes containing 5-15 nmole of a lipid such as DDAB or DOPE (as described above) form a complex with 1 .mu.g plasmid, without forming visible large aggregates. Inspection for visible large aggregates is typically performed without the aid of a microscope. The endpoint of the titration of the amounts of lipid and nucleic acid is also achieved by assaying for increased transfection efficiency, either in vitro or in vivo, as compared to a non-stabilized control (as described

below).

Detail Description Paragraph:
[0098] To keep the lipid:nucleic acid complexes from forming large aggregates and losing transfecting activity with time, two approaches are taken: (1) incorporating a small amount of a hydrophilic polymer such as PEG-PE (approx. 1% mole ratio) into lipid:nucleic acid complexes within a few minutes after their preparation; and/or (2) condensing the nucleic acid with a polycation such as a polyamine (e.g., approximately 0.05 to 5.0 nmole of spermidine per .mu.g DNA) prior to mixing with the liposomes. The optimal amount of the polyamines and hydrophilic polymer can be determined by one of skill in the art by titrating the polyamine or hydrophilic polymer with the nucleic acid so that the formed complexes do not form large, e.g., visible, aggregates. The size of these lipid:nucleic acid complexes can be estimated by dynamic light scattering to be in the range of 410.+-.150 nm. The endpoint of the titration is also achieved by assaying for increased transfection efficiency either in vitro or in vivo, as compared to a non-stabilized control (as described below).

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L32: Entry 73 of 82 File: USPT Aug 7, 2001

DOCUMENT-IDENTIFIER: US 6271206 B1
TITLE: Sonic nebulized nucleic acid/cationic liposome complexes and methods for pulmonary gene delivery

Detailed Description Text (6):
A "stabilizing agent" within the context of the present invention may be any compound or material that, when complexed to a nucleic acid molecule, permits ultrasonic nebulization of the complex without significant loss of transfection efficiency of the nucleic acid. Loss of the supercoiled form (the most potent and fragile of plasmid physical forms) upon nebulization should be less than 20%. Suitable stabilizing agents include one or more lipids, peptides and/or polymers. For example, a peptide/DNA complex containing a condensing peptide (GM208) and a lytic peptide (GM225.1) formulated at a charge ratio (-:+:-) of 1:3:1 is stable after nebulization, as indicated by particle size and zeta potential measurements. Lipids are preferred stabilizing agents, and cationic lipids, such as N-[1-(2,3-dioleyloxy)propyl]-N-N-N-trimethylammonium chloride (DOTMA), are particularly preferred. Cationic lipids are typically employed with helper lipids (or co-lipids) that facilitate the release of DNA from the endosomes following endocytic uptake of the nucleic acid/lipid complex by fusing with endosomal membranes and modulating their physical state. Suitable co-lipids include dioleylphosphatidylethanolamine (DOPE) and/or cholesterol (Chol) (see Brigham et al., Am. J. Med. Sci. 298:278-281, 1989; Canonica et al., Am. J. Resp. Cell. Mol. Biol. 10:24-29, 1994; Bennett et al., Biosci. Rep. 15:47-53, 1995). Lipids for use in the present invention may generally be obtained from commercial sources, such as Avanti Polar Lipids Inc. (Alabaster, Ala.).

Other Reference Publication (8):
Schwarz et al., "Delivery of DNA-Cationic Liposome Complexes by Small-Particle Aerosol," Human Gene Therapy 7: 731-741, 1996.

Other Reference Publication (9):
Tomlinson and Rolland, "Controllable gene therapy Pharmaceutics of non-viral gene delivery systems," Journal of Controlled Release 39: 357-372, 1996.

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L37: Entry 30 of 39 File: USPT Jan 13, 2004

DOCUMENT-IDENTIFIER: US 6677313 B1
**** See image for Certificate of Correction ****
TITLE: Method for gene therapy using nucleic acid loaded polymeric microparticles

Detailed Description Text (56):
It is possible to incorporate nucleic acid molecules into liposomes or complexed to liposomes which are then incorporated into the microparticles for delivery to cells. The ratio of liposome to polymer solution is important in determining whether the liposomes will remain as separate entities during the process for incorporation into the microparticles. If the ratio of solvent is too high, the phospholipid will dissolve into the polymer solvent, rather than remaining as part of the liposome bilayer. This is a function of the liposome composition, polymer concentration, and solvent composition. The liposomes can increase the efficiency of the transfer of the DNA into the cells when the liposomes are released from the microparticles. Liposomes are commercially available from Gibco BRL, for example, as LIPOFECTIN.RTM. and LIPOFECTACE.RTM., which are formed of cationic lipids such as N-[1-(2,3 dioleyloxy)-propyl]-n,n,n-trimethylammonium chloride (DOTMA) and dimethyl dioctadecylammonium bromide (DDAB). Numerous methods are also published for making liposomes, known to those skilled in the art.

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L41: Entry 27 of 39 File: USPT Dec 27, 1994

DOCUMENT-IDENTIFIER: US 5376369 A
TITLE: Vaccine adjuvant

Abstract Text (1):
This invention is directed to an adjuvant composition in the form of an emulsion which is comprised of an emulsion-forming amount of a non-toxic tetra-polyol or of a POP-POE block polymer and an immunopotentiating amount of a muramyldipeptide of the formula: ##STR1## or a pharmaceutically acceptable salt thereof, where R and R.sub.1 are each independently H or acyl of 1 to 22 carbon atoms, R.sub.2 is optionally substituted alkyl or optionally substituted aryl, R.sub.3 is H, alkyl, or aryl, R.sub.4 is H or lower alkyl, X is L-alanyl, L-.alpha.-aminobutyryl, L-arginyl, L-asparginyl, L-aspartyl, L-cysteinyl, L-glutaminyl, L-glutamyl, glycyl, L-histidyl, L-hydroxyprolyl, L-isoleucyl, L-leucyl, L-lysyl, L-methionyl, L-ornithinyl, L-phenylalanyl, L-prolyl, L-seryl, L-threonyl, L-tyrosyl, L-tryptophanyl, or L-valyl, and Y is D-glutamine, D-isoglutamine or D-isoasparagine. This invention is also directed to a vaccine containing an antigen and an adjuvant composition of the invention. This invention is also directed to a process of preparing an adjuvant composition and a vaccine of the invention. This invention is also directed to a kit for extemporaneous preparation of an adjuvant composition and a vaccine of the invention.

Brief Summary Text (3):
This invention relates to improved vaccine adjuvant compositions, improved processes for preparing said adjuvant compositions, and methods of using the improved compositions.

Brief Summary Text (5):
Adjuvants are useful for improving the immune response obtained with any particular antigen in a vaccine. Although some antigens are administered in vaccines without an adjuvant, there are many antigens that lack sufficient immunogenicity to stimulate an useful immune response in the absence of an effective adjuvant. Adjuvants also improve the immune response obtained from "self-sufficient" antigens, in that the immune response obtained may be increased or the amount of antigen administered may be reduced.

Brief Summary Text (7):
A number of naturally occurring compounds such as the lipid-A portion of gram negative bacteria endotoxin and trehalose dimycolate of mycobacteria have been tried as substitutes for FCA and FIA. Also, the phosholipid lysolecithin has been shown to have adjuvant activity (B. Arnold et al., Eur. J. Immunol., 9:363-366 (1979)). In addition, several synthetic surfactants, for example, dimethyldioctadecyl ammonium bromide (DDA) and certain linear polyoxypropylene-polyoxyethylene (POP-POE) block polymers (available commercially under the trademark Pluronic.RTM.) have been reported as having adjuvant activity (H. Snippe et al, Int. Archs. Allergy Appl. Immun., 65, 390-398 (1981)). R. Hunter et al. have reported in J. Immunol., 127, 1244-1250 (1981) that POP-POE block polymers increase antibody formation to bovine serum albumin (BSA) in mice when used as the surfactant component of an mineral oil/water emulsion adjuvant formulation. While these natural and synthetic surfactants demonstrate-some degree of adjuvanticity, they for the most part fail to achieve the degree of immunopotentiation obtained

using FCA or FIA.

Brief Summary Text (16):
Another aspect of the invention is a vaccine, comprising an adjuvant composition of the invention in combination with an immunogenic amount of an antigen.

Brief Summary Text (19):
Another aspect of the invention is a kit for the preparation of a vaccine of the invention, which differs from the adjuvant kit described above in that an immunogenic amount of an antigen is added to the second container, or present in a third container.

Brief Summary Text (20):
Another aspect of the invention is a method for inducing an immune response in an animal having an immune system, which method comprises administering a vaccine of the invention.

Brief Summary Text (34):
(iii) relieving the disease, i.e., causing regression of the disease. (It should be noted that vaccination may effect regression of a disease where the disease persists due to ineffective antigen recognition by the subject's immune system, where the vaccine effectively presents antigen.)

Brief Summary Text (40):
An "emulsion-forming amount" of a non-toxic metabolizable oil is that amount which will form an emulsion in the presence of the tetra-polyol or POP-POE block polymer. The oil component of the adjuvant compositions and vaccines of the invention will usually be present in an amount between 1% and 30%, but preferably in an amount between 1% and 10%. It is most preferred to use about a 5% concentration of oil.

Brief Summary Text (44):
The term "antigen" as used herein also includes combinations of haptens with a carrier. A hapten is a portion of an antigenic molecule or antigenic complex that determines its immunological specificity, but is not sufficient to stimulate an immune response in the absence of a carrier. Commonly, a hapten is a relatively small peptide or polysaccharide and may be a fragment of a naturally occurring antigen. In artificial antigens, it may be a low molecular weight substance such as, for example, an arsanilic acid derivative. A hapten will react specifically in vivo and in vitro with homologous antibodies or T-lymphocytes. Haptens are typically attached to a large carrier molecule such as bovine serum albumin (BSA) or keyhole limpet hemocyanin (KLH) by either covalent or non-covalent binding before formulation as a vaccine. For example, a common artificial antigen used to test vaccines and adjuvants consists of 2,4-dinitrophenol (DNP) covalently bound to BSA. Suitable antigens for use in this invention include antigens for hepatitis B, influenza, AIDS and herpes.

Brief Summary Text (45):
The term "immunogenic amount" of an antigen refers to an amount of antigen sufficient to stimulate a useful immune response, when administered with an adjuvant of the invention. The amount of antigen necessary to provide an immunogenic amount is readily determined by one of ordinary skill in the art, e.g., by preparing a series of vaccines of the invention with varying concentrations of antigen, administering the vaccines to suitable laboratory animals (e.g., guinea pigs), and assaying the resulting immune response by measuring serum antibody titer, antigen-induced swelling in the skin, and the like.

Brief Summary Text (60):
Another aspect of the invention is a vaccine comprising an adjuvant composition of the invention in combination with an immunogenic amount of an antigen. Suitably this is a vaccine in the form of an emulsion having oily particles dispersed in a

continuous aqueous phase, for immunizing an animal, which vaccine comprises an immunogenic amount of an antigen; an emulsion-forming amount of a non-toxic tetra-polyol or a non-toxic POP-POE block polymer; optionally, an emulsion-forming amount of a non-toxic metabolizable oil; optionally, an emulsion-stabilizing amount of a glycol ether-based surfactant; water or aqueous solution; and an immunopotentiating amount of a muramyldipeptide, preferably a derivative of formula (I). A preferred subgenus is the vaccine which includes a tetra-polyol, especially where said tetra-polyol is Tetronic.RTM. 1501. Another preferred subgenus is the vaccine which includes a POP-POE block polymer, wherein said block polymer is Pluronic.RTM. L121. A preferred class of the subgenus is the vaccine wherein substantially all of the volume of the oily particles in the adjuvant composition is present in particles having a diameter less than about 800 nm, preferably less than about 300 nm. Another preferred class is the vaccine wherein said muramyldipeptide derivative of formula (I) is N-acetyl-muramyl-L-threonyl-D-isoglutamine. Another preferred class is the vaccine wherein said muramyldipeptide derivative of formula (I) is N-acetylmuramyl-L-alanyl-D-glutamine butyl ester. A preferred subclass of these classes is the adjuvant composition which includes a non-toxic metabolizable oil, wherein said oil is squalene or squalane. Another preferred subclass is the adjuvant which includes a glycol ether-based surfactant, wherein said surfactant is Tween.RTM. 80. A presently preferred embodiment is the vaccine which comprises Tetronic.RTM. 1501 in an amount between 1% and 10%; squalane or squalene in an amount between 1% and 10%; Tween.RTM. 80 in an amount of about 0.2%; isotonic buffered saline; and N-acetylmuramyl-L-threonyl-D-isoglutamine in an amount between 0.0001% and 10%, especially where substantially all of the volume of the oily particles in the adjuvant composition is present in particles having a diameter less than about 800 nm, preferably less than about 300 nm. Another preferred embodiment is the vaccine which comprises Pluronic.RTM. L121 in an amount between 1% and 10%; squalane or squalene in an amount between 1% and 10%; Tween.RTM. 80 in an amount of about 0.2%; isotonic buffered saline; and N-acetyl-muramyl-L-threonyl-D-isoglutamine in an amount between 0.0001% and 10%.

Brief Summary Text (62):
Another aspect of the invention is a process for preparing the adjuvant composition or vaccine of the invention, which process comprises mixing together the aqueous phase and the emulsion-forming amount of the non-toxic tetra-polyol or of the POP-POE block polymer so as to form an emulsion.

Brief Summary Text (65):
Another aspect of the invention is a kit for extemporaneous preparation of a vaccine of the invention, which kit comprises a first container containing an emulsion having oily particles dispersed in a continuous aqueous phase, where said emulsion comprises Tetronic.RTM. 1501 or Pluronic.RTM. L121, squalane or squalene, optionally Tween.RTM. 80, and isotonic buffered saline; and a second container containing N-acetylmuramyl-L-threonyl-D-isoglutamine in powder form (preferably lyophilized), or in aqueous solution or suspension, and an immunogenic amount of an antigen; where the concentrations of the components in each container are selected such that combination of the contents of both containers produces an vaccine composition comprising Tetronic.RTM. 1501 or Pluronic.RTM. L121 in an amount of 1-10%, squalane or squalene in an amount between 1% and 10%, Tween.RTM. 80 in an amount of about 0.2%, N-acetylmuramyl-L-threonyl-D-isoglutamine in an amount between 0.0001% and 10%, an immunogenic amount of an antigen, and isotonic buffered saline. Optionally, the antigen can be in a separate third container. A preferred subgenus is the kit which includes Tetronic.RTM. 1501. Another preferred subgenus is the kit which includes Plutonic.RTM. L121. A preferred class of both subgenera is the kit wherein substantially all of the volume of the oily particles in the adjuvant composition is present in particles having a diameter less than about 800 nm, preferably less than about 300 nm.

Brief Summary Text (66):
Another aspect of the invention is a kit for extemporaneous preparation of a

vaccine of the invention, which kit comprises a first container containing the emulsion of the tetra-polyol or POP-POE block polymer in the aqueous phase and a second container containing the antigen, wherein the muramyldipeptide may be present in a third container, or in the first or second containers.

Brief Summary Text (68):
Another aspect of the invention is a method for inducing an immune response in an animal having an immune system, which method comprises administering a vaccine comprising an immunogenic amount of an antigen; an emulsion-forming amount of a non-toxic tetra-polyol or of a non-toxic POP-POE block polymer; optionally, an emulsion-forming amount of a non-toxic metabolizable oil; optionally, an emulsion-stabilizing amount of a glycol ether-based surfactant; water or aqueous solution; and an immunopotentiating amount of a muramyldipeptide derivative of formula (I) ##STR5## or a pharmaceutically acceptable salt thereof, wherein R and R.sub.1 are each independently H or acyl of 1 to 22 carbon atoms; R.sub.2 is alkyl or aryl, optionally substituted with halo, nitro, or lower alkyl; R.sub.3 is H, alkyl, or aryl; R.sub.4 is H or lower alkyl; X is L-alanyl, L-.alpha.-aminobutyryl, L-arginyl, L-asparginyl, L-aspartyl, L-cysteinyl, L-glutaminyl, L-glutamyl, glycyl, L-histidyl, L-hydroxyprolyl, L-isoleucyl, L-leucyl, L-lysyl, L-methionyl, L-ornithinyl, L-phenylalanyl, L-prolyl, L-seryl, L-threonyl, L-tyrosyl, L-tryptophanyl, or L-valyl; and Y is D-glutamine, D-isoglutamine or D-isoasparagine. A preferred class is the method which includes a non-toxic tetra-polyol, especially where said tetra-polyol is Tetronic.RTM. 1501. Another preferred class is method which includes a non-toxic POP-POE block polymer, especially where said polymer is Pluronic.RTM. L121. A preferred subclass is the method wherein substantially all of the volume of the oily particles in the adjuvant composition is present in particles having a diameter less than about 800 nm, preferably less than about 300 nm. A presently preferred embodiment is the method for inducing an immune response in an animal having an immune system, which method comprises administering a vaccine comprising Tetronic.RTM. 1501 in an amount between 1% and 10%; squalane or squalene in an amount between 1% and 10%; Tween.RTM. 80 in an amount of about 0.2%; isotonic buffered saline; N-acetylmuramyl-L-threonyl-D-isoglutamine in an amount between 0.0001% and 10%; and an immunogenic amount of an antigen. Another presently preferred embodiment is the method for inducing an immune response in an animal having an immune system, which method comprises administering a vaccine comprising Plutonic.RTM. L121 in an amount between 1% and 10%; squalane or squalene in an amount between 1% and 10%; Tween.RTM. 80 in an amount of about 0.2%; isotonic buffered saline; N-acetylmuramyl-L-threonyl-D-isoglutamine in an amount between 0.0001% and 10%; and an immunogenic amount of an antigen.

Brief Summary Text (76):
Adjuvant compositions of the invention are prepared by emulsification, using a mixer. If an adjuvant composition is to be prepared on a laboratory scale using a tetra-polyol for immediate use, it may be mixed simply by hand. For example, Tween.RTM. 80 and buffered saline are added to squalane and Tetronic.RTM. 1501 in a test tube at 2.times. concentration, and the combination mixed using a vortex mixer to form an emulsion. To this is added a 2.times. solution of antigen and a muramyldipeptide derivative of formula (I) in buffered saline to form the completed vaccine. It is more preferred to use a high-shear mixer such as a Greerco Homogenizer Mixer to form a smoother, more homogenous emulsion.

Brief Summary Text (83):
The adjuvant compositions and vaccines of the invention are generally administered by injection, particularly intramuscular injection, preferably into a large muscle.

Brief Summary Text (84):
In general, an initial vaccination is administered using the desired antigen and an adjuvant composition of the invention. The vaccination is "boosted" several weeks later (usually 2-6 weeks, for example, 4-6 weeks) using a vaccine of the invention

with or without (preferably with) the MI)P component. Generally, 1-2 mL of a vaccine (such as are described in the Examples below) is administered to a human subject in the practice of the invention.

Detailed Description Text (12):
To Compositions 1-5 was then added solid N-acetylmuramyl-L-threonyl-D-isoglutamine (Thr-MDP) to a concentration of 500 .mu.g/mL, to form the complete adjuvant "concentrate." The concentrate was then mixed with a 2.times. concentration solution of antigen (ovalbumin in saline, 1 mg/mL) to form a test vaccine.

Detailed Description Text (13):
Composition 6 did not receive any Thr-MDP prior to mixing with a 2.times. concentration solution of antigen (ovalbumin in saline, 1/mg mL) to form a test vaccine.

Detailed Description Text (15):
Each test vaccine (0.2 mL) was administered to 8 female guinea pigs. At four weeks following administration, each animal was boosted with the same test vaccine (but without the Thr-MDP). Antibody titer was measured from serum samples collected at weeks 4 and 6 after initial administration. At 6 weeks, each animal received ovalbumin intradermally, and the diameter of the erythema, and the infiltration rating were determined after 24 hours, as an indication of cell-mediated immunity.

Detailed Description Text (41):
J. Vaccines

Detailed Description Text (42):
Vaccines of the invention are prepared by adding an appropriate amount of antigen to any of the compositions described above. Suitable antigens include antigens for hepatitis B, influenza (for example, A or B), AIDS and herpes. The vaccine may contain more than one antigen if desired, for example, antigens for diphtheria, pertussis, and tuberculosis may be coadministered in a single composition.

Detailed Description Text (43):
For ease of preparation, a small portion of the PBS used may be withheld from the adjuvant preparation, e.g., one may prepare the adjuvants described above using 90 mL rather than 100 mL, and use the withheld PBS to dissolve/suspend the antigen(s). The antigen/PBS solution is then mixed with the (slightly) concentrated emulsion to prepare the final vaccine. Alternatively, and more preferably, an adjuvant emulsion (without MDP) of two times concentration is mixed with an antigen/MDP solution of two times concentration.

Detailed Description Text (47):
Two times concentrated emulsions, consisting of 10% v/v squalane, 5% v/v Pluronic.RTM. L121 and 0.4% polysorbate 80 in phosphate buffered saline, were used in the test, having been prepared as for Composition 4 (Example 1). One emulsion was stored frozen for seven days before use, while the other was freshly prepared and kept at room temperature. On the day vaccines were prepared, Thr-MDP was added to the fresh and thawed emulsions. Equal volumes of 2.times. concentrated ovalbumin were added to the 2 lots of emulsions just before the vaccines were used to immunize groups of 8 female guinea pigs. The final concentrations of the constituents of the vaccines were: Phosphate buffered saline 92.33%; Squalane 5%; Pluronic.RTM. L121, 2.5%; Polysorbate 80, 0.17%; Thr-MDP 250 .mu.g/ml; and Ovalbumin 1.0 mg/ml.

Detailed Description Text (48):
Guinea pigs were vaccinated on days 0 and 28 with 0.2 ml of vaccine per animal, bled on days 28 and 42, and skin tested with 10 .mu.g of ovalbumin on day 42.

Detailed Description Text (51):

Hepatitis Virus Vaccine

Detailed Description Text (52):
Groups of 8 female Hartley guinea pigs were immunized subcutaneously with a vaccine consisting of Hepatitis B virus surface antigen (HBsAg) in adjuvant (prepared as for Composition 4, Example 1, without refrigeration) or adsorbed to alum (commercially available hepatitis vaccine). The HBsAg in saline and HBsAg adsorbed to alum were provided by Merck Sharpe and Dohme Research Laboratories. The vaccine formulation consisted of 92.33% PBS, 5% squalane, 2.5% Pluronic L121, 0.17% polysorbate 80, 100 .mu.g/ml Thr-MDP, and either 1.0 .mu.g/ml or 0.2 .mu.g/ml of HBsAg. Each animal received 0.5 ml of vaccine at day 0 and week 4. The animals were bled at weeks 4, 6 and 15. Antibody titers were determined by ELISA techniques and were far superior for the vaccine of the invention.

Detailed Description Text (54):
Influenza Virus Vaccine

Detailed Description Text (55):
Groups of 10 or 11 6-7 week old female BALB/cJ mice were immunized subcutaneously with a vaccine consisting of influenza virus antigen in adjuvant (prepared as for Composition 4, Example 1, without refrigeration). The adjuvant formulation consisted of 2.5% Pluronic.RTM. L121, 5.0% squalane, 0.17% Tween.RTM. 80, 500 .mu.g/ml Thr-MDP, and PBS qs. The influenza virus strains used were A/Taiwan, A/Leningrad and B/Ann Arbor. The antigen concentration is expressed in .mu.g/mL of hemagglutinin (HA). The vaccine was diluted so that the mice received a 0.01 .mu.g/mL of HA of each strain in 0.1 ml of the adjuvant. One group of mice was given adjuvant only. The groups of mice were immunized as follows:

Detailed Description Text (63):
The ovalbumin vaccine of Example 4 was prepared as described in Composition 4, Example 1, but without the Tween.RTM. 80.

Detailed Description Text (65):
The ovalbumin vaccine of Example 4 was prepared as described in Composition 4, Example 1, but the vaccine composition contained only 1.25% Pluronic.RTM. L121.

Detailed Description Text (67):
Other Vaccines

Detailed Description Text (68):
The ovalbumin vaccine of Example 4 was prepared as described in Composition 4, Example 1, but using the following antigens in place of ovalbumin:

Detailed Description Text (97):
The weight of MDP in the vaccine was subject to minor variation depending on the species of animal tested. In some cases, the emulsion was not refrigerated before addition of the MDP and antigen.

Detailed Description Text (99):
A. Preparation of Vaccine

Detailed Description Text (100):
An ovalbumin vaccine was prepared as follows: 2.5% Tetronic.RTM. 1501, 5.0% squalane, 0.2% Tween.RTM. 80, qs phosphate buffered saline (pH 7.4) were added to a test tube and vortex-mixed until a milky emulsion was obtained. This emulsion was then passed through a Microfluidizer.RTM. four times. 250 .mu.g/mL of solid N-acetyl-muramyl-L-threonyl-D-isoglutamine (Thr-MDP) was then added to the emulsion to form a 2.times. concentration emulsion of the adjuvant formulation. This formulation was then mixed with a 2.times. concentration solution of ovalbumin in saline to form the vaccine.

Detailed Description Text (102):
A group of 8 female Sim:(HA) guinea pigs, 350 g to 400 g, were injected subcutaneously in the nuchal region with 0.2 mL of the vaccine. Each animal received 200 .mu.g ovalbumin in the vaccine on Day 0, and 50 .mu.g ovalbumin in the vaccine on Day 28. The animals were bled by cardiac puncture on Days 28 and 42, and skin tested on Day 42 with 10 .mu.g ovalbumin, given intradermally. The diameter and induration of the skin tests were measured 24 and 42 hours later as an indication of cell-mediated immunity. The antibody titers were determined by passive hemagglutination and by ELISA. The results are reported in the Tables below. Each entry represents the mean obtained from the 8 animals. Infiltration was scored visually, on a 1 to 3 scale (1 being the weakest respose and 3 being a very obvious swelling at the skin test site.)

Other Reference Publication (1):
"Formulation of Vaccine Adjuvant Muramyldipeptides. 3. Processing Optimization Characterization, and Bioactivity of an Emulsion Vehicle", Pharmaceutical Research (1989), No. 9, vol. 6, pp. 748-752.

CLAIMS:

17. A method for inducing an immune response in an animal having an immune system, which method comprises:

administering a vaccine comprising an immunogenic amount of an antigen; a non-toxic tetra-polyol in an emulsion-forming amount of between 0.2% and 49%; optionally, a non-toxic metabolizable oil in an emulsion-forming amount of up to 15%; optionally, a glycol ether-based surfactant in an emulsion-stabilizing amount up to 5%; water or aqueous solution; and a muramyldipeptide derivative of formula (I) ##STR8## or a pharmaceutically acceptable salt thereof, wherein R and R.sub.1 are each independently H or acyl of 1 to 22 carbon atoms;

R.sub.2 is alkyl or aryl, optionally substituted with halo, nitro, or lower alkyl;

R.sub.3 is H, alkyl, or aryl;

R.sub.4 is H or lower alkyl;

X is L-alanyl, L-.alpha.-aminobutyryl, L-arginyl, L-asparginyl, L-aspartyl, L-cysteinyl, L-glutaminyl, L-glutamyl, glycyl, L-histidyl, L-hydroxyprolyl, L-isoleucyl, L-leucyl, L-lysyl, L-methionyl, L-ornithinyl, L-phenylalanyl, L-prolyl, L-seryl, L-threonyl, L-tyrosyl, L-tryptophanyl, or L-valyl; and

Y is D-glutamine, D-isoglutamine or D-isoasparagine, in an immunopotentiating amount of between 0.0001% and 10%.

18. The method of claim 17 wherein said vaccine comprises:

a tetrapolyol in an amount of between 1% and 10%, wherein said tetrapolyol has a polyoxypropylene base of molecular weight between 6500 and 7000 and has polyoxyethylene in an amount between 1% and 10% of said tetrapolyol;

squalane or squalene in an amount of between 1% and 10%;

polyoxyethylene 20 sorbitan monooleate in an amount of about 0.2%;

isotonic buffered saline;

N-acetylmuramyl-L-threonyl-D-isoglutamine in an amount of between 0.0001% and 10%; and

an immunogenic amount of an antigen.

19. A vaccine for immunizing an animal, which vaccine comprises an immunogenic amount of an antigen and an adjuvant composition in the form of an emulsion having oily particles dispersed in a continuous aqueous phase, which adjuvant composition comprises:

a non-toxic tetra-polyol in an emulsion-forming amount of between 0.2% and 49%;

optionally, a non-toxic metabolizable oil in an emulsion-forming amount of up to 15%;

optionally, a glycol ether-based surfactant in an emulsion-stabilizing amount of up to 5%;

water or aqueous solution; and

a muramyldipeptide derivative of formula (I) ##STR9## or a pharmaceutically acceptable salt thereof, wherein R and R.sub.1 are each independently H or acyl of 1 to 22 carbon atoms;

R.sub.2 is alkyl or aryl, optionally substituted with halo, nitro, or lower alkyl;

R.sub.3 is H, alkyl, or aryl;

R.sub.4 is H or lower alkyl;

X is L-alanyl, L-.alpha.-aminobutyryl, L-arginyl, L-asparaginyl, L-aspartyl, L-cysteinyl, L-glutaminyl, L-glutamyl, glycyl, L-histidyl, L-hydroxyprolyl, L-isoleucyl, L-leucyl, L-lysyl, L-methionyl, L-ornithinyl, L-phenylalanyl, L-prolyl, L-seryl, L-threonyl, L-tyrosyl, L-tryptophanyl, or L-valyl; and

Y is D-glutamine, D-isoglutamine or D-isoasparagine, in an amount of between 0.0001% and 10%.

20. The vaccine of claim 19 wherein said tetra-polyol has a polyoxypropylene base of molecular weight between 6500 and 7000 and has polyoxyethylene in an amount between 1% and 10% of said tetra-polyol.

21. The vaccine of claim 20 wherein said muramyldipeptide derivative of formula (I) is N-acetylmuramyl-L-threonyl-D-isoglutamine.

22. The vaccine of claim 20 wherein said muramyldipeptide derivative of formula (I) is N-acetylmuramyll-alanyl-D-glutamine butyl ester.

23. The vaccine of claim 21 which comprises:

a tetrapolyol in an amount of between 1% and 10%;

squalane or squalene in an amount of between 1% and 10%;

polyoxyethylene 20 sorbitan monooleate in an amount of about 0.2%;

isotonic buffered saline; and

N-acetylmuramyl-L-threonyl-D-isoglutamine in an amount of between 0.0001% and 10%.

24. The vaccine of claim 23 wherein substantially all of the volume of said oily particles in said adjuvant composition is present in particles having a diameter

less than about 800 nm.

25. The vaccine of claim 24 wherein substantially all of the volume of said oily particles in said adjuvant composition is present in particles having a diameter less than about 300 nm.

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L41: Entry 30 of 39 File: USPT Jun 25, 1991

DOCUMENT-IDENTIFIER: US 5026546 A
TITLE: Stabilized adjuvant suspension comprising dimethyl dioctadecyl ammonium bromide

Abstract Text (1):
A stabilized aqueous adjuvant suspension of dimethyl dioctadecyl ammonium bromide stabilized with at least 0.1 part by weight of a polymer of acrylic acid crosslinked with polyallyl sucrose per part by weight of dimethyl dioctadecyl ammonium bromide, plus

Abstract Text (2):
a method of stabilizing vaccines adjuvanted with such dimethyl dioctadecyl ammonium bromide.

Brief Summary Text (2):
It is known that DDA is an excellent adjuvant for various vaccines. However, a disadvantage of the use of DDA is its poor solubility in water, suspensions of DDA are not stable in water, flocculate rapidly and cannot be restored by shaking.

CLAIMS:

1. A stabilized aqueous adjuvant suspension comprising dimethyl dioctadecyl ammonium bromide stabilized with at least 0.1 part by weight of a polymer of acrylic acid crosslinked with polyallyl sucrose per part by weight of dimethyldioctadecyl ammonium bromide.

2. In a method of stabilizing vaccines adjuvanted with dimethyldioctadecyl ammonium bromide, the improvement comprising stabilizing the adjuvant solution through addition of at least 0.1 part by weight of a polymer of acrylic acid with polyallyl sucrose per part by weight of dimethyl dioactadecyl ammonium bromide.

3. A suspension as claimed in claim 1 further comprising approximately 1 part by weight of a polymer of acrylic acid crosslinked with a polyallyl sucrose per part by weight of dimethyl dioactadecyl ammonium bromide.

4. A suspension as claimed in claim 1 further comprising 0.1 mg of dimethyl dioctadecyl ammonium bromide and 0.1 mg of a polymer of acid crosslinked with polyallyl sucrose per ml of aqueous suspension.

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L45: Entry 17 of 17 File: USPT Sep 21, 1999

DOCUMENT-IDENTIFIER: US 5955077 A
TITLE: Tuberculosis vaccine

Brief Summary Text (65):
Various methods of achieving adjuvant effect for the vaccine include use of agents such as aluminum hydroxide or phosphate (alum), commonly used as 0.05 to 0.1 percent solution in phosphate buffered saline, admixture with synthetic polymers of sugars (Carbopol) used as 0.25 percent solution, aggregation of the protein in the vaccine by heat treatment with temperatures ranging between 70.degree. to 101.degree. C. for 30 second to 2 minute periods respectively. Aggregation by reactivating with pepsin treated (Fab) antibodies to albumin, mixture with bacterial cells such as C. parvum or endotoxins or lipopoly-saccharide components of gram-negative bacteria, emulsion in physiologically acceptable oil vehicles such as mannide mono-oleate (Aracel A) or emulsion with 20 percent solution of a perfluorocarbon (Fluosol-DA) used as a block substitute may also be employed. According to the invention DDA (dimethyldioctadecylammonium bromide) is an interesting candidate for an adjuvant, but also Freund's complete and incomplete adjuvants as well as QuilA and RIBI are interesting possibilities.

Brief Summary Text (86):
The efficacy of such a "DNA vaccine" can possibly be enhanced by administering the gene encoding the expression product together with a DNA fragment encoding a polypeptide which has the capability of modulating an immune response. For instance, a gene encoding lymphokine precursors or lymphokines (e.g. IFN-.gamma., IL-2, or IL-12) could be administered together with the gene encoding the immunogenic protein, either by administering two separate DNA fragments or by administering both DNA fragments included in the same vector.

Detailed Description Text (30):
The experimental vaccines which contained 100 mg ST-CF/dose and applied dimethyldioctadecylammonium bromide (DDA) (250 mg/dose) as adjuvant in 0.2 ml were given S.C. three times with weekly intervals at different sites on the back of the mice to boost a strong cellular immune response to ST-CF.

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